REMARKS/ARGUMENTS

Claims 1 to 91 are pending in the application. No claims are added, canceled, or amended herein.

In the Office Action dated May 6, 2003, all pending claims were rejected under 35 U.S.C. § 103. Applicants again respectfully traverse the rejections, on the grounds that the Examiner has failed to establish a *prima facie* case of obviousness.

Summary of Invention

As described at length in the specification, the present invention relates to methods for screening for compounds that are agonists or antagonists of *Ret-independent* intracellular signaling mediated by GPI-anchored receptors. In preferred embodiments, the GPI-anchored receptors are GFRα receptors. *See* page 3, lines 15 to 20. The invention derives from Applicants' surprising discovery of a novel GFRα-mediated signaling pathway for GDNF in Ret (-/-) nervous system cells.

Response to Rejections

In the Office Action dated May 6, 2003, the rejection of claims 1 to 6, 16 to 21, 30, 32, 39, 40 and 42 under Section 103 over Ibanez (WO 97/18240), in view of Jefferies (U.S. Patent No. 5,981,194) and Baloh (PNAS 95:5801-5806, 1998) was maintained. Applicants again respectfully traverse this rejection, and incorporate herein by reference the arguments made against this rejection in the response submitted on March 24, 2002. In the interest of brevity, these arguments will not be reiterated in their entirety, but rather will be expanded upon in the discussion to follow, to once again show that these references fail to establish the *prima facie* obviousness of the claimed invention.

As the Office Action appears to appreciate, Ibanez describes methods for identifying compounds which are GDNF homologs, comprising incubating cells which express c-RET receptors with a test compound, and determining whether intracellular signaling has been effected in the cells. The step of "determining whether signaling has been effected" may comprise, for example, looking for increased survivability in the cells. *See e.g.,* Ibanez, claim 14. This method is based, at least in part, upon the discovery reported in Ibanez that "the c-RET receptor tyrosine kinase is a signal transducing receptor for GDNF." *See* Ibanez,

page 18, lines 7 to 8. There is simply nothing in Ibanez to suggest that GDNF can mediate intracellular signaling in the absence of Ret.

To overcome this deficiency, Ibanez has been combined with Baloh.[1] Baloh reiterates the knowledge in the prior art that GDNF and neurturin (NTN) are both known to signal through a receptor system that includes a GPI-linked GFα receptor ***and*** Ret receptor tyrosine kinase, whereas the receptor for a related neurotrophic growth factor, persephin (PSP), is unknown. *See* Baloh page 5801, col. 2, 2nd paragraph. Baloh also reports on the identification and characterization of a third GPI-linked GFα receptor, namely GFRα3. *See* Baloh page 5801, col. 2, 3rd paragraph. Having identified this GFα receptor, Baloh goes on to conduct experiments to determine whether Ret-GFRα3 complexes may form functional receptors for PSP or any of the other known GF ligands. *See* Baloh page 5805, col. 1, 2nd paragraph. However, on the basis of these experiments, Baloh reports:

> although GFRα3 is similar in structure to GFRα1 and GFRα2, it does not form a signaling receptor complex with Ret for any of the known ligands and may therefore have an as yet unknown ligand or require the presence of additional proteins to take part in GF signaling.

See id. In other words, Baloh teaches that although the authors have identified the GFRα3 receptor, they do not know what ligand the receptor binds, nor what intracellular pathway it may use for downstream signaling.

In the Discussion section of the paper, Baloh addresses what conclusions may possibly be drawn from the experimental results. Specifically, Baloh states, as the Office Action correctly notes:

> [o]ur analysis of transfected fibroblasts indicates that GFRα3 does not form a functional receptor complex with Ret for any of the known GF ligands. There are several possibilities to explain this result, all of which suggest the presence of additional receptor system components. We cannot exclude the possibility that known GF ligands interact with GFRα3 in the presence of another Ret-like signaling protein. The existence of another Ret-like signaling molecule has also been proposed to explain the expression of GFRα1 and GFRα2 in several structures without Ret [citation omitted]. Alternatively, GFRα3 may mediate Ret signaling for an as yet unknown ligand of the GDNF family. Finally, the lack of PSP interaction with any known receptor complex suggests either an additional coreceptor or signaling component is required to mediate PSP signaling.

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1 Applicants note that Baloh, based upon a publication date of May, 1998, is available as prior art to the instant application under Section 102(a), and reserve the right to antedate the reference.

See Baloh, page 5806, col. 1, 2nd paragraph. Again, Baloh has not identified any Ret-independent signaling pathway for any of the known GF-ligands, but merely proposes that one ***might*** exist.

It appears to be the Examiner's position that the teachings of Ibanez and Baloh could be combined by one of ordinary skill in the art to arrive at the methods of the present invention. Applicants respectfully, but vehemently, disagree. Ibanez teaches that GDNF signals through a GF (*i.e.*, GPI-linked) receptor system that requires Ret. Baloh reiterates this teaching. However, Baloh goes on to state that an additional GF receptor has been identified, GFRα3, but that this receptor does not complex with Ret to initiate signaling for any of the known GF ligands (*i.e.*, GDNF, NTN and PSP). Applicants respectfully submit that on the basis of this teaching one **cannot** conclude, as has been done in the Office Action, that GFRα3 signals in a Ret-independent manner. Indeed, Baloh does not even draw that conclusion. Rather, Baloh states that the experimental results ***may mean*** that there is another Ret like protein (or additional components) required for GFRα3 signaling. Moreover, Baloh indicates that it is ***equally likely*** that the results mean that GFRα3 is the receptor for an unknown GF ligand other than GDNF, NTN or PSP.[2] Thus, at best, Baloh may suggest that one might try to identify an alternative, Ret-independent, signaling pathway for GFRα3, ***but Baloh does not conclude, and provides no evidence, that such a pathway actually exists.***

Moreover, even if one were to accept Baloh's invitation to search for a Ret-independent signaling pathway for GFRα3, instead of adopting Baloh's suggestion to search for another GF ligand (which, as referenced in footnote 2 is the path chosen by Baloh), neither Baloh nor Ibanez provides any teaching that would enable one of ordinary skill in the art to determine that Ret-independent intracellular signaling effected by GPI-anchored receptors has actually been agonized or antagonized. It is only by resorting to the teaching of the instant application that one may understand that intracellular Ca^{2+} concentration, or kinase activation, or any of the other end-points specifically described in the specification, are correlated with the Ret-independent signaling pathway that underlies Applicants' invention.

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2 In fact, subsequent to the Baloh article cited by the Examiner, those authors did identify that "other GF ligand" that they had suggested might exist. The ligand, now known as "artemin," was shown by Baloh to signal **through the GFRα3-RET receptor complex!** *See* Baloh, R.H. et al., "Artemin, a novel member of the GDNF ligand family, supports peripheral and central neurons and signals through the GFRα3-RET receptor complex," *Neuron*, **1998,** *21*, 1291-1302 (cited in IDS submitted May 16, 2000)

Thus, the combination of Ibanez and Baloh fail to provide an enabling teaching of Applicants' invention, as is required to establish a *prima facie* case of obviousness under Section 103. *See Rockwell International v. U.S.*, 147 F.3d 1358, 1365 (Fed. Cir. 1998); *In re Payne*, 606 F.2d 303, 314 (CCPA 1979) (holding tht the references relied on to support an obviousness rejection :must provide an enabling disclosure, *i.e.*, they must place the claimed invention in the possession of the public.").

Resort to Jefferies fails to overcome this deficiency. Jefferies is directed to the GPI linked protein p97, which is completely unrelated to GFRα. *See* Jefferies, col. 6, lines 14-15. Thus, Applicants respectfully submit that contrary to the assertions in the Office Action, the mere mention in Jefferies that compounds identified by the methods described therein may be relevant to Alzheimer's disease fails to provide the proper motivation for one of ordinary skill in the art to combine Jefferies with either Ibanez or Baloh. Why would the skilled artisan looking for further information regarding GFRα signaling pathways consult a reference directed to signaling of p97?

Moreover, even if one of skill in the art were to consult Jefferies, that reference fails to make up for the deficiencies in Ibanez and Baloh discussed above. Jefferies describes two methods for identifying stimulants, agonists or antagonists of p97. The first comprises incubating a test compound with a cell capable of expressing p97, and measuring the amount of p97 expressed. Alternatively, Jefferies teaches that one may incubate a cell expressing p97 on its surface in the presence of iron and a test compound, and measure the amount of iron uptake in the cell. *See* Jefferies, col. 8, lines 30 to 48 and col. 25, lines 38 to 48. Applicants fail to understand how Jefferies could possibly aid the skilled artisan armed with Ibanez and Baloh in understanding how to determine that Ret-independent signaling through GFRα3 has been effected. Certainly not by measuring iron uptake, or expression of p97.

It is therefore clear that Ibanez, Baloh and Jefferies, even if improperly combined, fail to put the skilled artisan in possession of the invention defined by claims 1 to 6, 16 to 21, 30, 32, 39, 40 and 42. Although Baloh may suggest that Ret-independent signaling pathways for GFRα3 *may* exist, and may even suggest that experiments be performed to identify such pathways, neither that reference nor Ibanez and/or Jefferies contain any fruits of that search, which would be required to enable Applicants' invention. It is only by resorting to the teachings of the instant application that one of ordinary skill in the art is enabled to practice

the claimed invention. It is the Applicants, not the prior art, who have shown that GDNF can signal through GPI-linked GFRα receptors in cells not expressing Ret, and that such signaling results in an increase in intracellular Ca^{2+}, Src kinase activation, and the other down-stream events set forth in the instant application. Accordingly, Applicants respectfully submit that the Office Action has failed to establish a *prima facie* case of obviousness, and respectfully request that the rejection over Ibanez, Baloh and Jefferies be withdrawn.

The remaining claims, which introduce additional elements relating, for example, to specific end-points that may be assayed to determine that Ret-independent signaling has been effected, are rejected under Section 103 as the result of combinations of Ibanez, Baloh and Jefferies with one or more of Shen (J. Immun. 152:3017-3023, 1994), Dikic (Nature 383:547-549, 1996), Finkbeiner (Neuron 19: 1031-1047, 1997), and Chalazonitis (Developmental Biol. 204:385-406, 1998). Applicants again traverse these rejections, and respectfully submit that the combinations made in crafting these rejections is improper.

Shen, for example, is cited for teaching that intracellular signaling is measured as an increase in calcium concentration and/or kinase activation. *See* Office Action at 6. Shen teaches that activation of the macrophage receptor FcγRIIA results in phosphorylation on tyrosine of a set of cellular substrates (e.g. PLC-γ1), and $[Ca^{2+}]_i$ flux. *See* Shen, paragraph bridging pages 3020 and 3021. As a preliminary matter, Applicants note that Shen is directed to a signaling pathway in *macrophages*, not in nervous system cells, which are called for in several of the pending claims, and are the subject of Ibanez and Baloh. No explanation is provided in the Office Action as to why one armed with Ibanez and Baloh, and looking to elucidate Ret-independent GFRα3 signaling pathways in nervous system cells (which is, after all, the motivation suggested by Baloh, and adopted in the Office Action), would be motivated to look to a reference directed to signaling pathways in macrophages.[3]

Moreover, even if Shen may teach one of ordinary skill in the art that changes in $[Ca^{2+}]_i$ flux and kinase activation result from signaling through FcγRIIA, this knowledge in no way enables the practice of the instant invention. At best, *if* motivated by Ibanez and

3 It is further noted that the Office Action fails to even establish that FcγRIIA, the receptor being investigated in Shen, is a GPI-linked receptor. Certainly, this is not taught in the Shen article. The Examiner is respectfully requested to provide further evidence that this is the case. If it is the Examiner's position that this fact is generally known to those of skill in the art, the Examiner is respectfully requested to make this assertion for the record.

Baloh to look for a Ret-independent GFRα3 signaling pathways, instead of a new GF ligand, and *if* motivated to consult art directed to signaling pathways for a completely unrelated receptor, in a completely different cell types, one of ordinary skill in the art *might* be instructed by Shen that $[Ca^{2+}]_i$ flux and kinase activation *could conceivably* be end points of Ret-independent GFRα3 signaling pathways. But until experiments were done in cells expressing GFRα3 receptors, but not expressing Ret, that skilled artisan would have no way of knowing if that were true. Even then, absent the evidence provided in the instant application, one would not know if the increase in $[Ca^{2+}]_i$ flux resulted from signaling initiated through the GFRα3 receptor, or some other pathway. Thus, as discussed before, the references provide at best only an invitation to experiment, and could in no way put those of ordinary skill in the art in possession of the claimed methods, as would be required to render the claimed methods obvious. *See In re Payne*, 606 F2d at 314.[4] It is only after consulting the considerable evidence reported in the instant application that one can practice the claimed invention.

Without belaboring the point further, Applicants respectfully submit that the comments regarding Shen are equally applicable to each of the additional references that are added to the various Section 103 rejections as allegedly teaching the further elements set forth in additional dependent claims. Simply put, although these references teach possible end points for various signaling pathways, there is nothing in any of the references that teach that the end points are correlated with any specific GPI-receptor mediated Ret-independent signaling pathway. Certainly, none of these endpoints is correlated with the GFRα-mediated, Ret-independent signaling pathway that, starting with the teachings of Baloh and Ibanez,

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4 Attention is also directed to the recent holding by the CAFC in the case of *Elan Pharmaceuticals v. Mayo Foundation for Med. Education and Research*, 2003 U.S. App. LEXIS 20195. Although this opinion is in the context of anticipation, since a finding of obviousness requires that combined prior art relied upon "must provide an enabling disclosure," the guidance provided by the Federal Circuit should be equally applicable to the present case.

In *Elan*, the court held that even though the prior art may have foreseen that a transgenic mouse consistent with that claimed could be produced, in order to invalidate the claims, the prior art must teach one of ordinary skill in the art how to make or carry out the claimed invention *without undue experimentation.* Applicants respectfully submit that although it may be asserted that one of ordinary skill in the art, following the "suggestions" of the cited references, may have eventually been able to practice the methods enabled by the instant application (which assertion applicants submit respectfully is factually and legally untenable), to do so would have, at the very least, required undue experimentation. Accordingly, we respectfully submit that the references, even in combination, fail to provide an enabling disclosure, such that the claimed invention is nonobvious.

provides the basis for the rejections. Thus, these additional references serve merely as isolated teachings of possible avenues for further research. They do not, however, overcome the deficiencies in the primary references, with which they have been arbitrarily combined.

In view of the foregoing, it is clear that the prior art cited in the Office Action, in any proper combination, fails to establish the *prima facie* obviousness of Applicants' claimed invention. Accordingly, Applicants again respectfully request that the rejections under Section 103 be withdrawn, and that a Notice of Allowance for all of pending claims 1 to 91 be issued.

CONCLUSION

In the event that the Examiner is not persuaded that the application is in condition for allowance, the Examiner is invited to telephone Applicants' undersigned representative to resolve any outstanding issues.

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